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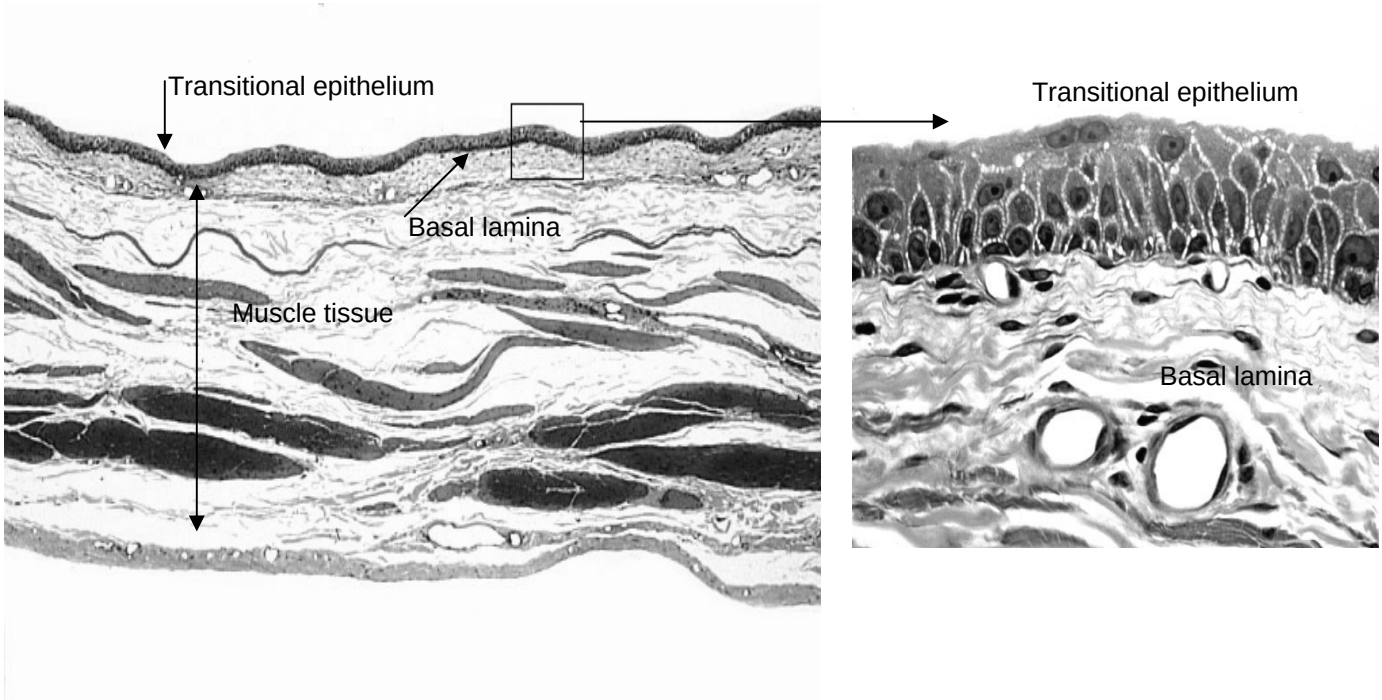
Bladder Cancer: An Example of Genetic Susceptibility Interacting with Exposure to Risk Factors

Bladder cancer accounts for approximately five percent of all cancers in Montana.[1] There are about 240 new cases diagnosed in Montana each year and an average of 45 deaths. This is consistent with the incidence and mortality rates of bladder cancer for the United States as a whole.[2]

The bladder is particularly vulnerable to the action of carcinogens because of its structure, function, and histology. It is lined with the transitional epithelium, made up of several layers of epithelial cells that protect the deeper tissues of the bladder (the connective tissue, called the basal lamina, and the muscle layers) from the caustic effects of urine and the damaging action of any toxins or carcinogens that might be present in the urine. The transitional epithelium constantly produces new cells from its lower layers as old cells from the surface in contact with the urine are shed. The kidneys clear many toxins from the body and excrete them into the urine. The bladder holds urine at varying concentrations for varying periods of time. This creates the potential for the cells lining the bladder to be exposed to a number of carcinogens.



[1] Montana Central Tumor Registry. 2008. *Cancer in Montana 2002-2006. An Annual Report of the Montana Central Tumor Registry*. Available online at www.cancer.mt.gov
[2] http://seer.cancer.gov/statfacts/html/urinb.html

More than 90% of bladder cancers are transitional cell carcinomas. As long as these tumors remain confined to the transitional epithelium and do not penetrate the basal lamina, they are classified as *in situ*. About half of transitional cell carcinomas of the bladder are *in situ,* a quarter are local, and a quarter are regional or distant. The remaining kinds of bladder cancer are squamous cell carcinomas (~3%), adeno-carcinomas (cancer of glandular and secretory cells) (~1%), and a few other very rare subtypes.

The incidence and mortality rates of bladder cancer are three to four times higher in men than women.[1,2] Differences in occupational exposures to potential carcinogens and in the prevalence of smoking probably explain most of the sex difference. The incidence of bladder cancer is four to seven times higher in smokers than in non-smokers, and risk increases with intensity of smoking, measured as packs per day.[2,3]

Since the 1950s, investigators have documented increased risk for bladder cancer in many occupations, including individuals exposed to vehicle exhaust and people engaged in manufacturing and using industrial dyes, plastics, rubber, leather, and paints.[3] A common feature of many of the implicated occupations is exposure to a class of chemicals called aromatic amines, known to be powerful carcinogens.[2] Aromatic amines and their byproducts are also found in many commercial and consumer products (non-steroidal anti-inflammatory drugs and other pharmaceuticals, hair dyes and commercial dyes, paints and pigments, herbicides, photographic developer, corrosion inhibitors, additives to industrial lubricants, rat poison, and cigarette smoke).[2,3]

Risk factors have been identified for many cancers and some are quite powerful. Even for the strongest risk factors, many people exposed to them do not get cancer. The most obvious example is smoking cigarettes: 90% or more of all lung cancer is attributable to smoking, but many people who smoke do not develop lung cancer. One-third of all bladder cancer is attributable to smoking,[2,3] but not all patients with bladder cancer have a history of smoking and not all smokers develop bladder cancer.

Minor genetic variation in the ability to detoxify carcinogens may explain why some people exposed to them develop bladder cancer while others do not. The study of genetic variation in susceptibility to cancer is a relatively new area of research that advanced rapidly the under the influence of the Human Genome Project.[4] Genes contributing to increased risk of cancer cannot be modified but identification of environmental co-factors may point to prevention strategies. Because some alleles[5] that confer increased risk for cancer may be relatively uncommon in the population, because the increased risk may be small, and because increased risk may occur only in the presence of specific exposures, progress in this aspect of cancer research has been slow.[6] Studies must be very large or

[3] Silverman DT et al. 2006. Bladder Cancer. In D. Schottenfeld and JF Fraumeni, eds. *Cancer Epidemiology and Prevention*, 3rd ed. New York: Oxford University Press, pp. 1101-1127.
[4] http://www.ornl.gov/sci/techresources/Human_Genome/home.shtml
[5] Allele: a variant of a gene.
[6] Foulkes WD. 2008. *NEJM* 359:2143-2153.

investigators must rely on meta-analysis (the systematic statistical combination of results from many smaller studies) to look for increased genetic susceptibility to cancer.

Genetic susceptibility to cancer means that an individual may have an inherited biological risk of developing cancer. There are two general forms:

- Major chromosomal anomalies or single-gene mutations of high penetrance[7] that confer high risk of cancer
    - environmental or other external exposures exert relatively little influence on the risk of developing cancer
    - familial aggregation[8] of cancer may be obvious and usually follows simple patterns of inheritance
    - account for approximately five percent of cancers

- Polymorphic[9] variants of essentially normal genes that increase cancer risk in the presence of specific risk factors or exposures
    - environmental exposures exert more influence on the risk of developing cancer
    - familial aggregation of cancer may be less apparent unless family members also share exposure to risk factors through living situations and lifestyle choices

Many alleles suspected to confer increased risk of cancer may do so only in the presence of specific exposures. For example, N-acetyltransferase 2 (NAT-2) is an enzyme that participates in the detoxification of aromatic amines.[2,3] There are several alleles of NAT-2, creating multiple phenotypes,[10] classified as rapid acetylator, intermediate acetylator, and slow acetylator. The slow acetylator phenotype, which is less able to detoxify aromatic amines, is estimated to confer a 40% to 50% increased risk of bladder cancer. Not all individuals with the slow acetylator phenotype will get bladder cancer, in large part because they may have little or no exposure to aromatic amines.

Studies of NAT-2 and bladder cancer are the strongest evidence currently available that a common genetic variant interacting with a common environmental exposure increases the risk of cancer. The situation is no doubt more complex because allelic variants of several other genes also appear to increase or decrease the risk of bladder cancer in the presence of aromatic amines and other exposures.[11] Glutathione S-transferase M-1 (GSTM1) is

[7] High penetrance: most people with the allele show the effects of it.
[8] Familial aggregation: a disease obviously runs in families; close relatives of an affected person are much more likely than the general population to also have the disease.
[9] Polymorphism: existence of more than one allele (variant) of a given gene in a population; the least common allele must occur in at least 1% of the population.
[10] Phenotype: the expression and function of an individual's genetic makeup.
[11] Sanderson S et al. 2007. *Am J Epidemiol* 166:741-751; Chao C. et al. 2006. *Cancer Epidemiol Biomarkers Prev* 15:979-987; Figueroa JD et al. 2008. *Carcinogenesis* 29:1955-1962.

another enzyme that participates in the detoxification of aromatic amines. The GSTM1-null phenotype has little or no detoxifying function and is associated with increased risk of bladder cancer.[12]

Bladder cancer incidence and mortality have historically been about twice as high among white men as among men of other races in the United States.[3] Polymorphic differences in cancer susceptibility may explain some of the variation in racial and ethnic cancer incidence that used to be attributed to ill-defined "socioeconomic" factors. All human beings have the same basic genetic makeup, but the relative frequency of the various alleles of each gene often vary substantially by race, ethnicity, and geography. The slow acetylator phenotype is more common in white men (50%) than black men (35%) or Asian men (15%) in the United States.[13]

Other chemicals besides aromatic amines are also risk factors for bladder cancer, including gasoline and diesel combustion products and organic solvents.[2,3] In addition, chronic or recurrent bladder infections and bladder stones are risk factors. Infection with urinary schistosomiasis is also a risk factor although it is usually confined to Africa and Asia. Schistosomiasis is rarely seen in the United States except among recent immigrants or travelers returning from areas where it is endemic.[14,15]

Arsenic increases the risk of bladder cancer in areas where the arsenic concentration in drinking water is very high, usually above 200 micrograms per liter (ug/L) of water.[16] This generally occurs in Asia and South America. The World Health Organization international guideline and the current United States EPA standard for public water supplies in the United States is less than 10 ug/L (also expressed as 10 parts per billion).[17,18]

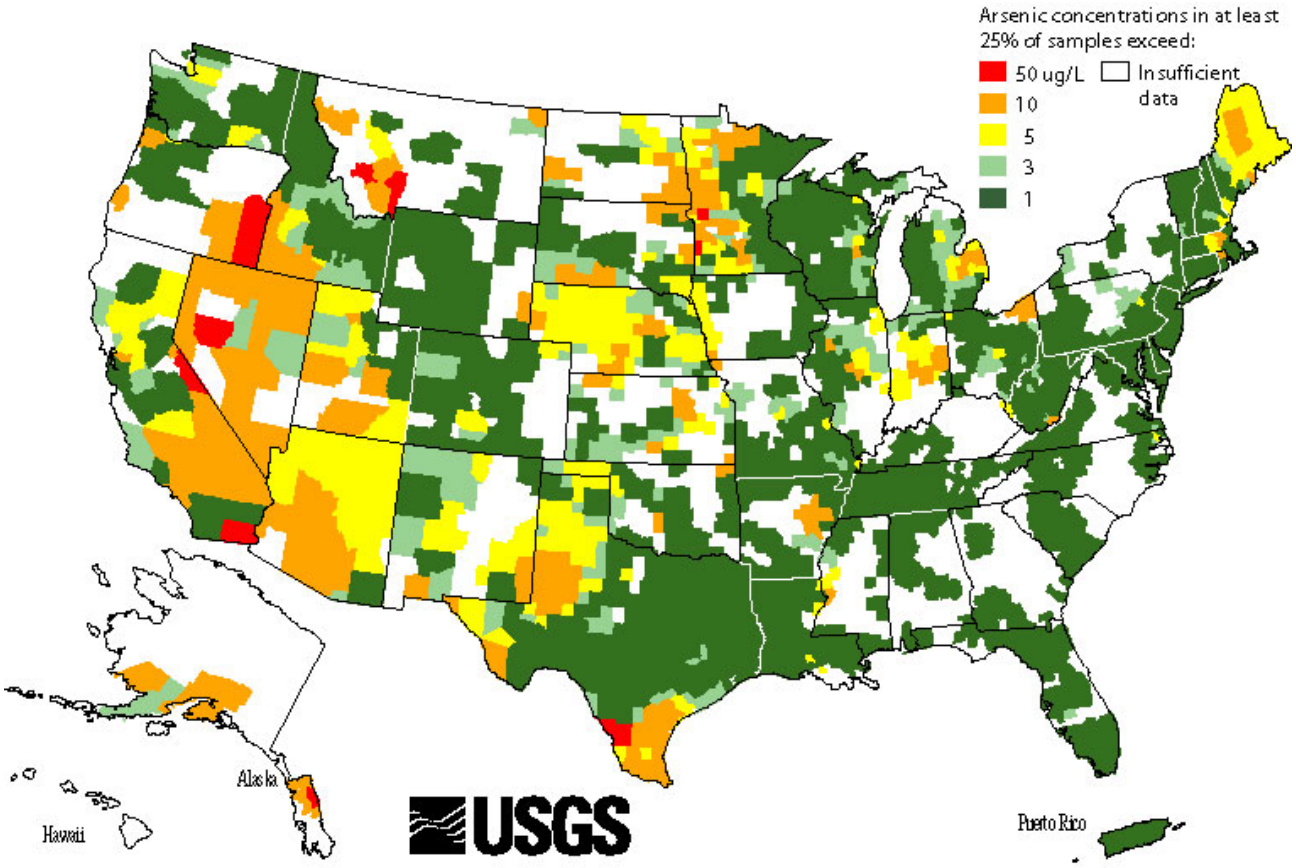
Some regions of the United States have groundwater arsenic concentrations greater than 10 ug/L, and even greater than 50 ug/L, in private wells, notably Michigan, Wisconsin, Minnesota, North Dakota, South Dakota, and New Hampshire.[19] These high concentrations occur primarily because of natural geologic conditions, although occasionally ground water supplies may be contaminated from agricultural or industrial sources.

By law, the content of arsenic in public water supplies in the United States must be below the 10 ug/L standard but this standard was only implemented in January, 2006.[14] From 1942 through 2005, the maximum permitted concentration of arsenic in public water supplies in the United States was 50 ug/L. There appears to be a latency period of 10 to

[12] Engel LS et al. 2002. *Am J Epidemiol* 156:95-109.
[13] Yu MC et al. 1994. *J Natl Cancer Inst*. 86:712-716; Muscat HE et al. 2008. *Biochem Pharmacol* 76:9290937.
[14] Maxwell-Parkin D. 2008. *Scan J Urol Nephrol* 26:1-9.
[15] http://www.cdc.gov/ncidod/dpd/parasites/schistosomiasis/default.htm
[16] http://www.atsdr.cdc.gov/toxprofiles/tp2.html#bookmark07 ; http://monographs.iarc.fr/ENG/Monographs/vol84/mono84-6.pdf
[17] http://www.who.int/mediacentre/factsheets/fs210/en/index.html
[18] http://www.epa.gov/safewater/arsenic/index.html
[19] http://water.usgs.gov/nawqa/trace/pubs/geo_v46n11/fig2.html

20 years for the effects of arsenic on bladder cancer. There is therefore ongoing interest in the effects of moderate concentrations of arsenic in drinking water because many people may have been exposed to concentrations of 10 to 50 ug/L before 2006.

The map below, from the United States Geological Survey,[19] shows the national distribution of arsenic in well water. Each colored block indicates that at least 25% of the wells tested in a county had a given concentration of arsenic. Blank areas indicate no testing, not necessarily the absence of arsenic.



On the whole, individual studies and meta-analyses have not found consistent evidence of increased risk for bladder cancer at exposure to arsenic in drinking water below 100 ug/L.[15,20,21] A large Danish cohort study found no increased risk of bladder cancer associated with arsenic concentration of drinking water between 0.05 and 25 ug/L, although the great majority of participants had arsenic exposures below 10 ug/L.[22] An

[20] Chu HA and Crawford-Brown DJ. 2006. *Int J Environ Res Public Health* 3:316-322.;
[21] Mink PJ et al. 2008. *Regul Toxicol Pharmacol* August 26, epub ahead of publication.
[22] Baastrup R et al. 2008. *Environ Health Perspect* 116:231-237.

ongoing study in New Hampshire, where many residents get drinking water from wells with arsenic concentrations in the range of 10 to 50 ug/L, found that patients with bladder cancer had a history of higher long-term arsenic intake, and that the combination of cigarette smoking and arsenic intake enhanced the risk of bladder cancer.[23]

In the United States, most chronic exposure to arsenic occurs in occupational settings, including smelting, wood preservation, electronics manufacture, and the manufacture and use of pesticides.[15]

The metabolism of arsenic is not well-understood, but it appears that a complex series of biologic reactions, each involving one or more enzymes, is involved in clearing arsenic from the body. Each of these enzymes is likely to have polymorphic variants which may make them more or less effective at clearing arsenic, so there are likely to be biological differences among individuals in their susceptibility to arsenic toxicity and carcinogenesis.[24]

The knowledge that there are genetic variations in the susceptibility to carcinogens helps explain why some people get cancer while others do not in spite of similar exposures. Each person probably has many alleles that confer greater or lesser susceptibility to cancer in his or her genetic makeup. We are still a long way from knowing, on a person by person basis, what those genetic risk factors are. Modification of genetic susceptibility is even farther away. The best strategy for reducing the risk of cancer is still to avoid known or suspected risk factors.

Please visit our website at www.cancer.mt.gov

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[23] Karagas MR et al. 2004. *Cancer Causes Control* 15:465-472.
[24] Steinmaus C et al. *J Toxicol Environ Heatlh A*. 70:159-170.; Chen YC et al. 2003. *Cancer Causes Control* 14:303-310.